UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,173	12/04/2008	Hitoshi Endou	65445(71526)	3295

21874 7590 01/04/2012

EDWARDS WILDMAN PALMER LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
STOICA, ELLY GERALD	
ART UNIT	**PAPER NUMBER**
1647	
MAIL DATE	**DELIVERY MODE**
01/04/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,173	ENDOU ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *5,6,15 and 16* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *5,6,15 and 16* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/04/2011 has been entered. Claims 5-6 and 15-16 are pending and are currently examined.

Withdrawn claim rejections

Claim Rejections - 35 USC § 112

2. The rejection of claims 5-6 and 8-14 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 103

3. The rejection of claims 5, 8-11, 12 and 14 under 35 U.S.C. 103(a) as being unpatentable over Endou et al. in view of Kanellis et al. and Hurteau et al. is withdrawn in view of the amendments to the claims.

Maintained and new claim rejections necessitated by amendment

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 6, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for screening for compounds that are used for treating a vascular disorder, does not reasonably provide enablement for methods of screening for compounds that are used for prevent a vascular disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 5,6,15 and 16 are drawn to a method of screening a substance efficacious for preventing vascular disorders, comprising using a cell line expressing URAT1 in the presence or absence of a test compound. However, the phrase "preventing a disorder",

given its broadest reasonable interpretation in light of the teachings in the specification, requires that absolutely no cell, nor tissue, or individual would present any symptom of a disorder after treatment with the identified compound. There is no evidence to date, either in the specification or in the prior art, that any compound identified by the screening method can accomplish this goal. The specification presents the results of experiments demonstrating that such modulators may treat vascular disorders. Nevertheless, there is no support for the prevention of any disorder or disease, as is required by the claims, with the modulators sought by the screening method. Neither can such support be obtained through reasonable extrapolation of the data or teachings in the art. Thus, in order to identify modulators to be used in prevention, the person of ordinary skill in the art would have to embark in a series of tedious experiments with very uncertain positive outcome and such experimentation is considered undue.

With regard to claim 6, which claims the performing of the method with umbilical vein epithelial cells, the art is not aware of the existence of such cells and as such, the method cannot be performed on inexistent cells. The existent term in the art is umbilical vein endothelial cells.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6 remain and claims 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, it is still not clear, in the independent claim 5 how the uric uptake **into** the cell can be at the same time elimination of the uric acid **in** the cell. Therefore, the metes and bounds of the claims could not be determined. A remedial solution could be elimination **from** a vascular muscle cell.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5, 6, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Endou et al. (CA 2456172- published 04/03/2003) in view of Kanellis et al. and Hurteau et al. (all cited in the previous Office actions).

The claims are drawn to methods of screening a substance for preventing or treating vascular disorders resulting from abnormal uric acid uptake into a vascular smooth muscle cell or abnormal uric acid elimination by URAT1 comprising positive taking steps such as measuring and comparing the uric acid levels, after contacting vascular muscle cells, in the presence and absence of a potential modulator. The cell may be an umbilical vein epithelial cell. Further, the method would discriminate between inhibitors and promoter of uric acid transfer.

Endou et al. teach a novel urate transporter gene participating in the urate transport in the kidney and a urate transporter which is a polypeptide encoded by the above gene (abstract). The protein product is named URAT1 and has the same amino acid sequence as the protein used in the instant Application. Furthermore, Endou et al. provides a screening method of a substance having modulatory action for the uric acid transport. The URAT1 works for transporting uric acid into the cells and is deeply

involved in the reabsorption of the uric acid. Also, as is shown in Figures 6, 8, 9 and 10, it is possible to quantify the accelerating or inhibiting action for uric acid uptake of the screening substance in the system where the URAT1 is expressed, by adding uric acid to the system, further adding the screening substance thereto, and comparing a uric acid uptake amount with that in the case with no addition of the screening substance. As is shown in Figures 6 and 8, the substances clinically used as uricosuric accelerators have remarkably inhibited the uptake of uric acid in the above experimental system, and thus, it is shown that it become possible to screen the uricosuric accelerating action of the screening substance in this system. As the cells used in this screening system, the cells are not limited to oocytes used in the experiments, and it is possible to use various living cells as long as the cells can express URAT1. The modulators identified can regulate the uptake of uric acid by the urate transporter involved in the urate transport in the kidney, and therefore can be used as an active ingredient of the medicines for the treatment/prevention of various diseases associated with the reabsorption of uric acid such as hyperuricemia and gout. It is possible to make the obtained active ingredient a pharmaceutical composition using a pharmacologically acceptable carrier (p.10-11). This may be used in humans, where hyperuricemia becomes a risk factor for cardiovascular diseases and hypertension (p.1).

Although Endou et al. teach that the method of screening may be performed using various living cells as long as the cells can express URAT1, they do not mention specifically vascular smooth muscle cells or HUVEC.

Kanellis et al. teach that soluble uric acid can induce vascular smooth muscle cells proliferation, activated through ERK, MAPK Cox-2 or PDGF pathways (introduction). By virtue of the effects of uric acid on vascular smooth muscle cells the uric acid must necessarily act through an uric receptor present at the membrane of cells. Also taught is that uric acid increases the production of MCP-1 protein in rat VSMC (p.1289, left col., last paragraph). The teachings of Kanellis et al. underscore the pathogenic role of uric acid in hypertension, vascular disease and atherosclerosis (p. 1292, left col. third paragraph).

Since the uric acid, in order to exert its effects, necessarily has to be transported in the cells by a transporting mechanism and, in view of Endou et al., this is through URAT1, identifying modulators of URAT1 can, in view of and Kanellis et al. be performed by proliferation assays in VSMC.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to employ the teachings of Kanellis et al. in the methods of Endou et al. with a reasonable expectation of success, because the assays were routinely used in the art and Kanellis et al. showed the usefulness of employing VSMC in finding modulators in uric acid pathogenesis. The choice of HUVEC is considered to be just another cell line for vascular cells and thus obvious to try by a skilled practitioner.

On pages 6-7 of the Remarks Applicant argues the method is not obvious over the art because a kidney cell is not a vascular muscle cell. The arguments were carefully considered but not found persuasive because as presented above, the Kanellis

et al. document based their work on vascular smooth muscle cells and the effect of the uric acid are necessarily mediated by the membrane receptor present on the cells.

On page 7 of the Remarks Applicant argues that none the cited reference teach that URAT1 is present on the surface of vascular smooth muscle cells. The arguments were carefully considered but not found persuasive because the URAT1, as a receptor for uric acid, is inherently present on the surface of the cells used by Kanellis et al.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5, 15 and 16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-6 of U .S. Patent No. 7,510,847 in view of Kanellis et al. (cited previously). The transporter used in the method of screening of the patent is the same and the method has the same outcome as in the instant Application. Even though the patent does not mention vascular smooth muscle cells, Kanellis et al. teach that soluble uric acid can induce vascular smooth muscle cells proliferation, activated through ERK, MAPK Cox-2 or PDGF pathways (introduction). Also taught is that uric acid increases the production of MCP-1 protein in rat VSMC (p.1289, left col., last paragraph). The teachings of Kanellis et al. underscore the pathogenic role of uric acid in hypertension, vascular disease and atherosclerosis (p. 1292, left col. third paragraph). Thus, it would have been obvious to performed the method claimed in the ‘847 patent on Vascular smooth muscle cells as taught by Kanellis et al. with a reasonable expectation of success , because the assays were

routinely used in the art and Kanellis et al. showed the usefulness of employing VSMC in finding modulators in uric acid pathogenesis.

On page 8 of the Remarks Applicant argues that nothing in the '847 Patent suggests using a vascular smooth muscle cell. The arguments were carefully considered but not found persuasive because as presented supra Kanellis et al. teaches the effect of uric acid on vascular muscle cells and inherently the effect is mediated by the receptor present on the cell.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 9:00-18:30 M-Th and 9:00-18:30 alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Elly-Gerald Stoica/
Primary Examiner, Art Unit 1647